Original Effective Date: 05/31/2023
Current Effective Date: 07/17/2025
Last P&T Approval/Version: 04/30/2025
Next Review Due By: 04/2026
Policy Number: C25204-A

Briumvi (ublituximab-xiiy)

PRODUCTS AFFECTED

Briumvi (ublituximab-xiiy)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. MULTIPLE SCLEROSIS:
   1. Documentation of a diagnosis of a relapsing form of multiple sclerosis, clinically isolated syndrome, or active secondary progressive multiple sclerosis
      AND

2. Documentation of screening for hepatitis B virus AND for patients who are negative for surface antigen [HBsAg] and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], documentation of a consult with a liver disease expert before starting treatment
   AND
3. (a) Documentation of **inadequate response (trial of 3 months) to ONE of the following: ONE of Interferon therapy (Avonex, Rebif, Extavia, Betaseron, Plegridy) OR Glatiramer OR formulary oral disease modifying therapy [e.g., Aubagio (teriflunomide), Tecfidera (dimethyl fumarate), Gilenya (fingolimod), etc.]
   **Inadequate response is defined as meeting at least TWO of the following three criteria during treatment: 1) Clinical relapses (at least two relapses within the past 12 months), 2) CNS lesion progression as measured by MRI, OR 3) Worsening disability (e.g. sustained worsening of EDSS score or neurological exam findings; worsening disability including, but not limited to, decreased mobility, decreased ability to perform activities of daily living due to disease progression, or EDSS > 3.5)
   OR
   (b) Documentation member has indicators of a highly active course of multiple sclerosis: (i) age of MS onset > 40 years of age, (ii) male gender, (iii) African American, (iv) motor, sphincter, brainstem-cerebellar symptoms, (v) MRI lesions in brainstem or spina cord, OR (vi) $\geq$ 2 acute relapses in first 2 years of onset with significant sustained disability following relapse
   AND
4. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Briumvi (ublituximab-xiiy) include: Active hepatitis B virus infection, history of life-threatening infusion reaction to Briumvi]
   AND
5. IF THIS IS A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of, or serious side effects to a majority (not more than 3) of the preferred formulary/PDL alternatives for the given diagnosis. Submit documentation including medication(s) tried, dates of trial(s) and reason for **treatment failure(s).
   **May be defined as meeting at least TWO of the following three criteria during treatment:
   1) Clinical relapses (at least two relapses within the past 12 months), 2) CNS lesion progression as measured by MRI, OR 3) Worsening disability (e.g., sustained worsening of EDSS score or neurological exam findings; worsening disability including, but not limited to, decreased mobility, decreased ability to perform activities of daily living due to disease progression, or EDSS > 3.5)

CONTINUATION OF THERAPY:

A. MULTIPLE SCLEROSIS:

1. Documentation of positive clinical response or stable disease based on ONE of the following:
   (a) Documentation of a stable number or decrease in acute attacks (relapses) within the last 6 months
   OR
   (b) Documentation of lack of progression or sustained disability
   OR
   (c) Recent (within last 6 months) MRI shows lack of development of new asymptomatic lesions
   AND
2. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity (e.g., serious opportunistic or recurrent infections, etc.)

DURATION OF APPROVAL:

Initial Authorization: 12 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a board-certified neurologist or a multiple sclerosis specialist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
150 mg IV infusion as a single dose, initially. A second 450 mg IV infusion is administered 2 weeks later. Then, 450 mg IV infusion 24 weeks following the first infusion, and every 24 weeks after that.

PLACE OF ADMINISTRATION:
The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

Note: Site of Care Utilization Management Policy applies for Briumvi (ublituximab-xiiy). For information on site of care, see Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous

DRUG CLASS:
Multiple Sclerosis Agents - Monoclonal Antibodies

FDA-APPROVED USES:
Indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Multiple sclerosis (MS) is a chronic, inflammatory, immune-mediated disease of the central nervous system (CNS) that disrupts communications within the brain and between the brain and body.
The mainstay of MS treatment are disease-modifying therapies (DMTs), which are designed to reduce the number of relapses, delay disease progression, and limit new disease activity as seen in MRI. Relapse frequency is measured using annualized relapse rate (ARR). Disability progression is often measured using the Expanded Disability Status Scale (EDSS).

Briumvi (ublituximab-xiiy) is a glycoengineered monoclonal antibody that targets CD20, a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ublituximab-xiiy results in cell lysis through mechanisms including antibody-dependent cellular cytolysis and complement-

dependent cytolysis. Glycoengineering is expected to enhance the potency of ublituximab.

FDA approval of Briumvi (ublituximab-xiiy) was based on the identical, double-blind, randomized, double-dummy, parallel-group, active-comparator– controlled and multicentered Phase 3 ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) trials, evaluating the safety and efficacy of Briumvi versus Aubagio in adults with RMS.

Patients were randomly assigned to receive either ublituximab-xiiy 150mg via intravenous infusion on day 1 and 450mg on day 15, followed by a 450mg dose every 6 months or teriflunomide 14mg orally, once daily. Both studies enrolled patients who had experienced at least one relapse in the previous year or two relapses in the previous 2 years or had the presence of a T1 Gd-enhancing lesion in the previous year.

Patients were also required to have an EDSS score of 0 to 5.5 at baseline. Neurological evaluations were performed at baseline, every 12 weeks, and at the time of a suspected relapse. Brain MRI scans were performed at baseline and at Weeks 12, 24, 48, and 96.

In the ULTIMATE I trial, the ARRs were 0.076 with Briumvi and 0.188 with Aubagio (relative reduction: 59%; P <0.001). In the ULTIMATE II trial, the ARRs were 0.091 and 0.178, respectively (relative reduction: 49%; P = 0.002).

The mean number of Gd-enhancing lesions was 0.016 in the Briumvi group and 0.491 in the Aubagio group (relative reduction: 97%; P <0.001) in the ULTIMATE I trial and 0.009 and 0.250, respectively (relative reduction: 97%; P <0.001), in the ULTIMATE II trial.

In the pooled analysis of the two trials, 5.2% of the participants in the Briumvi group and 5.9% in the Aubagio group had worsening of disability for ≥12 weeks at Week 96 (hazard ratio [HR], 0.84; 95% CI, 0.50 to 1.41; P = 0.51).

The endpoint of no evidence of disease activity (NEDA) was defined as no confirmed relapses, MRI activity, or worsening of disability. The percentage of patients with NEDA was 44.6% in the Briumvi group and 15.0% in the Aubagio group in the ULTIMATE I trial (odds ratio: 5.44; 95% CI: 3.54 to 8.38) and 43.0% in the Briumvi group and 11.4% in the Aubagio.

group in the ULTIMATE II trial (odds ratio: 7.95; 95% CI: 4.92 to 12.84) according to published results The most common adverse reactions reported with treatment included infusion reactions and upper respiratory tract infections.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Briumvi (ublituximab-xiiy) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Briumvi (ublituximab-xiiy) include: Active hepatitis B virus infection, a history of life-threatening infusion reaction to Briumvi.

Exclusions/Discontinuation:

Based on data from animal studies, Briumvi may cause fetal harm when administered to a pregnant woman. A pregnancy test is recommended in females of reproductive potential prior to each infusion with Briumvi. Advise females of reproductive potential to use effective contraception during Briumvi treatment and for 6 months after the last dose.

Prior to initiating Briumvi, perform testing for quantitative serum immunoglobulins. For patients with low serum immunoglobulins, consult immunology experts before initiating treatment with Briumvi.

Monitor the levels of quantitative serum immunoglobulins during treatment, especially in patients with opportunistic or recurrent infections, and after discontinuation of therapy until B-cell repletion. Consider discontinuing Briumvi therapy if a patient with low immunoglobulins develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

Because vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation until B-cell repletion, administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of Briumvi for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of Briumvi for non-live vaccines.

Member is not currently being treated with a disease modifying agent (DMA) other than the requested agent, B cell targeted therapy (e.g., rituximab, belimumab, ofatumumab), or lymphocyte trafficking blocker (e.g., alemtuzumab, mitoxantrone).

OTHER SPECIAL CONSIDERATIONS:

Administer Briumvi under the close supervision of an experienced healthcare professional with access to appropriate medical support to manage severe reactions, such as serious infusion reactions.

- First Infusion: 150 mg intravenous infusion
- Second Infusion: 450 mg intravenous infusion administered two weeks after the first infusion
- Subsequent Infusions: 450 mg intravenous infusion administered 24 weeks after the first infusion and every 24 weeks thereafter
- Observe the patient for at least one hour after the completion of the first two infusions. Post-infusion monitoring of subsequent infusions is at physician discretion unless infusion reaction and/or hypersensitivity has been observed in association with the current or any prior infusion.

MISSED DOSE: If a planned infusion is missed, administer as soon as possible; do not wait until the next scheduled dose. Reset the dose schedule to administer the next sequential dose 24 weeks after the missed dose is administered. Infusions must be separated by at least 5 months.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
J2329	Injection, ublituximab-xiiy, 1mg

AVAILABLE DOSAGE FORMS:

Briumvi SOLN 150MG/6ML single-dose vial

REFERENCES

1. Briumvi (ublituximab-xiiy) injection, for intravenous use [prescribing information]. Morrisville, NC: TG Therapeutics, Inc; October 2024.
2. Steinman L, et al. Ublituximab versus teriflunomide in relapsing multiple sclerosis. N Engl J Med. 2022;387(8):704–714. doi:10.1056/NEJMoa2201904
3. Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology Alexander Rae-Grant, Gregory S. Day, Ruth Ann Marrie, Alejandro Rabinstein, Bruce A.C. Cree, Gary S. Gronseth, Michael Haboubi, June Halper, Jonathan P. Hosey, David E. Jones, Robert Lisak, Daniel Pelletier, Sonja Potrebic, Cynthia Sitcov, Rick Sommers, Julie Stachowiak, Thomas S.D. Getchius, Shannon A. Merillat, Tamara Pringsheim Neurology Apr 2018, 90 (17) 789-800; DOI: 10.1212/WNL.0000000000005345
4. TG Therapeutics announces FDA approval of Briumvi™ (ublituximab-xiiy). News release. TG

Therapeutics. December 28, 2022. Accessed December 29, 2022. https://www.globenewswire.com/news-release/2022/12/28/2580377/8790/en/TG-Therapeutics-Announces-FDA-Approval-of-BRIUMVI-ublituximab-xiiy.html.

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Contraindications/Exclusions/Discontinuation References	Q2 2025
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Coding/Billing Information	Q2 2024
NEW CRITERIA	Q2 2023